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Late Mortality and Relapse following BuCy2 and HLA-Identical Sibling Marrow Transplantation for Chronic Myelogenous Leukemia

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Allogeneic hematopoietic stem cell transplantation (HSCT) is the only known curative therapy for chronic myelogenous leukemia (CML). Failure, because of relapse or nonrelapse mortality (NRM), generally occurs within 3 years of transplantation, but large studies with long-term follow-up are limited. We present mature results in 335 patients with CML who underwent allogeneic bone marrow transplantation (BMT) from HLA-identical siblings following busulfan and cyclophosphamide (BU/Cy2). Two hundred twenty-nine were in chronic phase (CP) and 106 in accelerated or blastic phase at transplantation. Median follow-up exceeded 14 years. The estimated probability of 18-year leukemia-free survival (LFS) for CP patients was 55.6% and for those beyond CP, 10.5%. Of 182 patients who survived leukemia-free at 3 years, the estimated probability of LFS at 18 years was 61.9%. Late relapse ($P = .039$) and late NRM ($P = .008$) occurred at higher rates in patients beyond CP at transplantation. There was no plateau in LFS.

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INTRODUCTION

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only proven curative therapy for chronic myelogenous leukemia (CML). Results of allogeneic transplantation in CML have been widely published, but median follow-up in most studies is 3 years or less [1-4]. Few large studies with prolonged follow-up after HSCT have been reported, and these have generally been limited by inclusion of patients with various diagnoses, preparative regimens, and sources and histocompatibility of donor cells. These studies report survival, but not leukemia-free survival (LFS) [5,6], providing the potential for overestimates of cure rates in CML, where patients may attain sustained survival following relapse [7,8]. Further, a single institutional study with prolonged follow-up reported a 15-year estimated cumulative relapse rate of only 8% for CML patients in chronic phase (CP) undergoing transplantation [9], substantially lower than that detected in studies with shorter follow-up [7,8,10].

We present the results of the most extended follow-up of a large cohort of patients with CML who underwent allogeneic bone marrow transplantation (BMT) from human leukocyte antigen (HLA)-identical sibling donors following busulfan and cyclophosphamide (Bu/Cy2), the most commonly used preparative regimen in this malignancy [11]. This report focuses on late relapse and death in patients in whom transplantation is commonly considered to have been successful, those alive, and leukemia-free 3 years following transplantation.

METHODS

Patients

All adults with CML who underwent allogeneic BMT from HLA-identical sibling donors following

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Bu/Cy2 at 4 centers in the United States and 3 in Australia, between March 1984 and December 1995, are included. Informed consent was obtained using forms approved by the institutional review board at each center. Data were analyzed as of January 1, 2008. One hundred fifteen patients were included in a report published in 1992 with a median follow-up of 3 years [2].

Clinical Care

All patients received identical preparation with Bu 1 mg/kg orally 4 times daily for 4 days followed by Cy 60 mg/kg intravenously on each of 2 days (Bu/Cy2) as previously described [2]. Bu doses were not adjusted to target plasma levels. BM from HLA-identical siblings was used as the source of HSC in every patient. Cyclosporine (CsA) or tacrolimus-based regimens were given to prevent graft-versus-host disease (GVHD). Prevention and treatment of infections and other supportive care measures were administered according to institutional guidelines.

Statistical Methods

Kaplan-Meier, cumulative hazard, and hazard rates were used to characterize overall survival (OS), relapse, and LFS. Kaplan-Meier methods were also used to assess the OS, relapse, and LFS for only those 182 subjects who survived 3 years leukemia-free. The log-rank test was used to compare CP, accelerated, and blastic phase patients. Univariate Cox proportional hazard regression was used to estimate the OS, relapse, and LFS hazard ratios for the following covariates: a 10-year increase in age, male versus female, disease phase XP accelerated, and blastic), acute GVHD (aGVHD), chronic GVHD (cGVHD), and interval from diagnosis to transplantation that was log transformed to the appropriate scale.

Smoothed hazard curves were generated by adjustment of the cumulative hazard into a continuous "smoothed" curve and then taking the derivative with respect to time. Multivariable Cox proportional hazard regression was used to estimate OS, relapse, and LFS hazard ratios. These same techniques were also used on the subgroup of patients that survived 3 years without disease. All relapses were hematologic or cytogenetic. Treatment of relapse was heterogeneous and varied over time and by institution. Primary cause of death was defined according to a published scheme [12]. Stata version 10.0 (Stata Corporation, College Station, TX) was used to run all analyses.

RESULTS

Patient Characteristics

A total of 335 consecutive adults with CML who underwent allogeneic HSCT from HLA-identical sibling donors at 7 institutions (Ohio State 88, Hahnemann 64, St. Vincent's 55, Wilford Hall 44, Cleveland Clinic 35, Alfred 33, and Royal Melbourne 16) were included in this analysis. Two hundred twenty-nine individuals were in CP, 62 in accelerated phase, and 44 in blastic phase at the time of transplantation. Table 1 summarizes the clinical characteristics of the study patients. Surviving patients were followed for a median of more than 14 years after transplantation.

OS and LFS from the Time of Transplantation

The 3-year OS from the time of transplantation for the entire group was 57.4% (95% confidence interval [CI]: 51.9 to 62.5%); the estimated probability of 18-year survival was 43.9% (95% CI: 37.9%-49.8%). The estimated 3- and 18-year LFS were 55.6% (95% CI: 50.1%-60.8%) and 34.4% (95% CI: 28.4%-40.5%). For chronic phase patients the OS at 3 years is 70.5% (95% CI: 64.1% - 76.0%) and 58.6% (95% CI 51.4%-65.1%) were estimated to survive at 18 years. LFS for CP patients was 68.8% (95% CI: 62.3%-74.4%) at 3 and 46.0% (95% CI: 38%-53.6%) at 18 years. For accelerated phase patients, 3-year OS and LFS were each 37.9% (95% CI: 25.6%-50%); estimated 18-year OS was 21.0% (95% CI: 10.5%-33.9%) and estimated probability of 18 year LFS was 17.5% (95% CI: 8.2%-29.7%). The 3-year OS for blastic phase patients was 15.9% (95% CI: 7.0%-28.0%), and 3-year LFS 13.6% (95% CI: 5.5%-25.4%); no blastic phase patients were estimated to survive at 18 years. The estimated probability that patients beyond CP at transplantation would be leukemia-free survivors at 18 years is 10.5% (95% CI: 5.2%-18.3%).

Relapse

The hazard rate for relapse fell sharply each year through year 5, and then remained low, but constant from years 6 through 14 (Figure 1). Twenty-seven (42.2%) of the 64 (hematologic or persistent cytogenetic) relapses occurred more than 3 years after transplantation. Thirty-three of the 37 patients (89.2%) who relapsed within 3 years (early) died, compared to 7 of 27 (25.9%) of those who relapsed beyond 3 years (late). (One patient relapsed 20 years following transplantation after data analysis was completed.) Death occurred less frequently ($P < .001$) and the interval

Table 1. Clinical Characteristics of 335 Study Patients

Age, median (range) in years	37	(18-58)
Sex, number (percentage) of females	152	(45.4)
Disease stage at transplant, number (%)		
Chronic phase	229	(68.3)
Accelerated	62	(18.5)
Blastic	44	(13.1)
Interval from diagnosis to transplant		
Median (range) in months	9	(1-210)

from relapse to death was longer ($P = .01$) in patients who relapsed late compared to those who relapsed early. The estimated cumulative incidence of late relapse for those patients who were alive and leukemia-free at 3 years is 22.8% (95% CI: 15.6%-32.6%); late relapse occurred in 32.5% of advanced phase and 21.4% of CP patients.

Survival and LFS for Patients Alive and Leukemia-Free at 3 Years

This report focuses on late (beyond 3 years) events after transplantation. Of the 182 patients (54.3% of those who underwent transplantation) alive and leukemia-free at 3 years, the estimated probability of 18-year OS is 77.0% (95% CI: 65.3%-83.6%) and of 18-year LFS is 61.9% (95% CI: 52.1%-70.3%) (Figure 2). The annual risk of failure (because of relapse or NRM) declined only very gradually beyond 3 years (Figure 3).

For 153 CP patients who were leukemia-free survivors at 3 years, the estimated probability of 18-year OS is 83.3% (95% CI: 75.0%-89.0%) and the18-year estimated probability of LFS 66.9% (95% CI: 56.1%-75.6%). The incidence of failure beyond 3 years remained significantly higher for patients who had advanced (accelerated or blastic) phase disease at transplantation compared to those in CP ($P = .001$).

Deaths Beyond 3 Years

Thirty-six patients who were alive and leukemia-free at 3 years died subsequently. The primary causes of death were cGVHD in 11, relapse in 7, new malignancy in 6, organ failure in 6 (pulmonary in 4), infection in 2, stroke in 1, accidental in 1, and unknown in 2. The cumulative incidence of developing a new malignancy was 10.4% (95% CI: 5.6%-19.1%) at 15 years. Five patients developed squamous cell and 2 basal cell skin carcinomas (SCC, BCC); 1 each developed Ewing sarcoma, colon cancer, endometrial carcinoma, cervical carcinoma, and a myeloproliferative disorder.

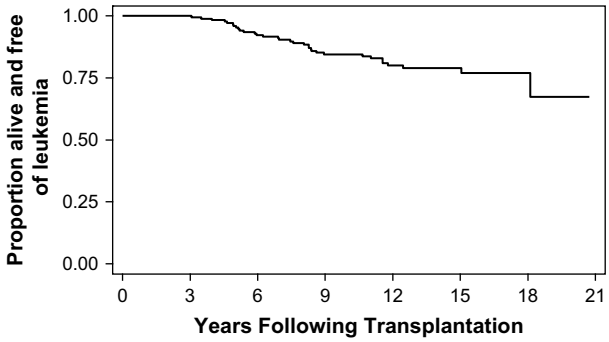

Figure 2. LFS of subjects who survived free of disease 3 years following transplantation.

Late NRM

The estimated cumulative incidence of late NRM is 18.1% (95% CI: 12.8%-24.5%), 40.6% in advanced phase patients, and 14.0% in CP patients ($P = .006$). The risk of NRM fell gradually beyond 3 years.

Prognostic Factors

Age, sex, disease phase, interval from diagnosis to transplantation, aGVHD, and cGVHD were evaluated in univariate analysis; results for all patients who survived leukemia-free at 3 years are presented in Table 2.

Multivariate analysis demonstrated that only advanced disease phase (hazard ratio [HR] 2.75, $P = .001$) and older age (HR 1.39, $P = .032$) were associated with significantly diminished LFS and OS (HR = 3.86, $P < .001$; HR 1.54, $P = .024$, respectively) of patients alive and leukemia-free at 3 years. Although aGVHD ($P = .005$) and longer interval from diagnosis to transplantation ($P < .001$) significantly influenced survival from day zero, they did not significantly influence survival of patients alive and leukemia-free at 3 years. cGVHD was associated with a significantly lower incidence of late relapse (HR = .30, $P = .002$), but not survival or LFS. Advanced disease phase was associated with a significantly increased rate of late relapse (HR 2.50, $P = .039$) and of late NRM (HR

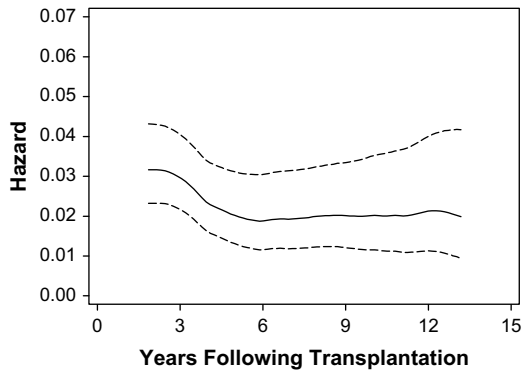

Figure 1. Smoothed hazard of relapse (——) including 95% CIs (——).

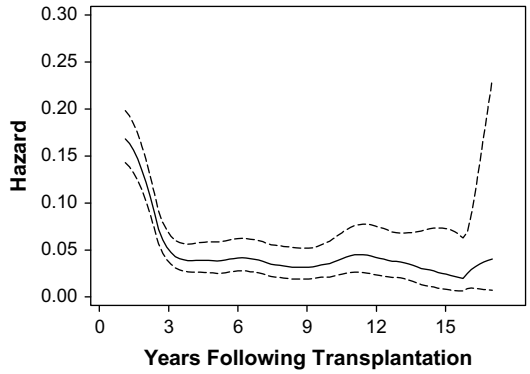

Figure 3. Smoothed hazard of failure (——) including 95% CIs (——).

Table 2. LFS Univariate Cox Regression for the Entire Dataset for Those Who Survived 3 Years without Disease

Variable	Hazard Ratio	*P*-Value	95%	Confidence Interval
Acute GVHD*	1.28	0.406	0.72	2.29
Chronic GVHD†	.75	0.353	0.42	1.37
Advanced phase‡	2.47	0.003	1.35	4.53
Male sex§	1.32	0.317	0.76	2.30
Age¶	1.32	0.085	0.96	1.80
Interval from diagnosis to transplantation⊥	1.20	0.285	0.86	1.69

GRHD indicates graft-versus-host disease; LFS, leukemia-free survival.
*Referent group is no aGVHD.
†Referent group is no cGVHD.
‡Referent group is chronic phase.
§Referent group is female.
¶Hazard ratio is for 10-year increase in age.
⊥Hazard ratio is for a 1 unit increase in the natural log of diagnosis to treatment time.

3.18, $P = .008$). Older age (HR 1.72, $P = .015$), was also associated with late NRM.

In multivariate analyses of CP patients alive and free of leukemia at 3 years, none of the variables included in this model were significantly predictive of survival or LFS. cGVHD was associated with a significantly lower incidence of late relapse (HR .29, $P = .004$), but not survival or LFS.

DISCUSSION

This study provides the longest published median follow-up of a large cohort of patients who underwent allogeneic BMT for CML at multiple institutions. The large number of patients and institutions ensures its broad applicability for patients undergoing allogeneic BMT with the Bu/Cy2 regimen.

This report focuses on late events in patients alive and leukemia-free 3 years following transplantation, a group for whom transplantation is commonly regarded as having been successful. Approximately 4 of every 5 such patients are estimated to be survivors at 18 years. Studies with less extended follow-up [1-6] and a remarkably low incidence of late relapse in 1 study with extended follow up [9] have led clinicians to infer that an overwhelming majority of patients alive and leukemia-free 3 years following transplantation are cured. The present study demonstrates a substantial incidence of late relapse and shows unequivocally that 3 or even 5 year relapse-free survival following transplantation for CML is not equivalent to cure. Nearly 2 of every 5 patients (1 in 3 of those transplanted with CP disease) who are alive and leukemia-free at 3 years will die or relapse over the next 15 years. Although expected mortality (deaths in an age-matched general population) may account in part for the absence of a plateau in mortality, such comparisons in other studies [5,6] and the transplant-related nature of many of the causes of late death in this cohort indicate that these patients are at higher risk of death than the general population. These data should ideally be compared to a nontransplant treatment cohort of CML patients for which mature data, unfortunately, does not exist. The study patients, with a median age of 37 years at transplantation, have a prolonged excess risk of mortality and a persistent risk of relapse. There is no plateau in LFS over the extended follow-up of this study. Furthermore, the excess risk of failure for patients with accelerated or blastic disease continues beyond 3 years and extended LFS occurred in only 10% of advanced phase patients.

Similar to other reports [7], late relapse of CML affected subsequent survival significantly less than early relapse. Nearly all patients who relapsed within 3 years, but only one-fourth of those relapsing beyond 3 years, died. The disparity suggests a biologic difference in the cells responsible for relapse, similar to that identified in acute lymphoblastic leukemia (ALL), where early relapse following standard chemotherapy appears to result from resistant, proliferative malignant clones, whereas late relapse occurs because of secondary events in leukemia stem cells [13].

It has been suggested that "current LFS" be reported following transplantation in CML to recognize patients who achieve sustained remissions and prolonged survival following relapse [8], as occurs commonly following imatinib and/or donor lymphocyte infusions (DLI) [14]. A substantial portion of the present study predated molecular monitoring and early detection and modern treatment of early relapse. Although it will not improve LFS, monitoring and early treatment of relapse will improve rates of "current LFS" and OS relative to the results reported here. In addition, improved supportive care has led to better survival in patients who undergo transplantation now compared to those in this study. Dose adjustment of Bu based on plasma levels improves results [4] and i.v. administration of Bu appears safer than oral administration [15], although its long-term benefit is not proved. Although Bu/Cy2 appears to be at least as safe and effective as radiation-based preparative therapy [2,3,11], the present data cannot exclude the possibility that there is a higher late relapse rate with Bu than with total body irradiation (TBI).

This analysis shows that only 3 of every 5 patients who are alive and relapse-free 3 years following an allo-transplantation for CML are alive and free of relapse another 15 years later and potentially cured. Late failure because of relapse or NRM is common. Although improvements in preparative regimens and posttransplant care result in better outcomes, the present study demonstrates that no plateau in LFS occurs following allo-transplantation, and cure is less common than is generally thought.

AUTHORSHIP

Contribution: E.A.C., P.A.C., B.R.A., and B.J.B. designed research; E.A.C., P.A.C., J.S., A.J.D., D.S, P.E., I.N.S., B.R.A., S.P., D.T., R.S., M.K., and B.J.B. performed research; E.A.C., G.P., P.E., I.N.S., B.R.A., and B.J.B. analyzed data, and E.A.C. wrote the paper.

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